Art Unit: 1632

Applicant's arguments filed January 14, 2008 have been fully considered but they are not persuasive. The amendment has been entered. Claims 92-104, 106-109, 111, 112, 114, 115 and 117-130 are pending.

Applicant's amendments have overcome the claim objections made in the office action mailed July 10, 2008.

The rejection made in the office action mailed July 10, 2007 under 35 U.S.C. § 112 first paragraph as lacking enablement because the claims lacked reference to a promoter or expression regulatory sequences is withdrawn in view of applicant's amendments to the claims.

The rejection of claim 92 in the office action mailed July 10, 2007 under 35 U.S.C. 112, second paragraph, with regards to "molecular biology methods" is withdrawn in view of applicant's amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-104, 106-109, 111, 112, 114, 115 and 117-130 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of a transgenic nonprimate mammal comprising transfecting a first nonprimate mammalian fibroblast cell or cell line with a transgene construct containing a first DNA sequence, selecting a transfected fibroblast into which said first DNA sequence operably linked to a promoter has been inserted into the genome of said first nonprimate mammalian fibroblast cell or cell line, performing a first nuclear transfer procedure of the same species as the fibroblast to generate a first transgenic nonprimate mammal at least heterozygous for said first DNA sequence, performing a biopsy or other cell selection

technique to obtain cells to establish a second nonprimate differentiated somatic cell or cell line from said first transgenic nonprimate mammal, characterizing said second nonprimate mammalian cell or cell line using molecular biology methods to ensure that the second nonprimate mammalian differentiated somatic cell or cell line is at lest heterozygous for said first DNA sequence, performing a second nuclear transfer procedure of the same species as the fibroblast with at least one cell of said second nonprimate mammalian differentiated somatic cell or cell one to produce at least a second nonprimate mammal at least heterozygous for said first DNA sequence, and producing the second transgenic nonprimate mammal or a method of preparing a genetically engineered transgenic mammal comprising inseminating a first female nonprimate mammal recipient with semen from a transgenic nonhuman primate of the same species known to have a transgene present and expressed, obtaining a transgenic nonprimate mammal embryo from said first female recipient, obtaining a somatic cell from said embryo, culturing said differentiated somatic cell in a suitable medium, such that a different somatic cell line is obtained, performing a nuclear transfer procedure of the same species as the donor cell with said differentiated somatic cell to produce at least one transgenic nonprimate mammal at heterozygous for said transgene, wherein said transgenic encodes a desired gene operably lined to a tissue specific promoter; and producing the transgenic nonprimate mammal, does not reasonably provide enablement for the breadth of the claims as presently written for reasons set forth in the office action mailed July 10, 2007. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, the art taught unpredictable results in the cloning of primates. The cloning of monkeys had only been successful using embryonic cells (Mitalipov, abstract).

Applicant argues the cloning of primates was enabled, citing Meng et al and Chan et al. Applicant argues any unpredictability would be within the realm of inoperative embodiments. These arguments are not persuasive.

Meng et al produced rhesus monkeys by nuclear transfer where a rhesus monkey blastomere is used as nuclear donor (Meng, page 455, col. 1, parag. 5, lines 1-3). Chan describes producing transgenic rhesus monkeys by a method not involving nuclear transfer. Thus, neither of these references overcomes the statement that Mitalipov that somatic cell nuclear transfer in monkeys had not been accomplished. This is not an inoperative embodiment, but an entire class of invention that was recognized by the art at the time of filing as lacking enablement. Applicant's invention is claimed as using a differentiated cell as nuclear donor, applicant's claims resemble much more Mitalipov's statement than the teachings of either Meng or Chan.

Further, the claims encompass cross-species nuclear transfer that is when the donor cell and oocyte are of different species. This was regarded by the art as lacking enablement at the time of filing.

Applicant argues the claims have been amended to reflect the cells or cell lines and the mammals are of the same species. This is not persuasive.

Applicant has amended the claims to state the donor cell and the resulting animal are of the same species. However, the donor cell, the recipient oocyte, and the surrogate mother must all be of the same species.

The issue surrounding transfection of cells, either to express a DNA sequence encoding a protein of interest or knocking out a gene of interest, is selection of the transfected cells. Nuclear transfer requires the donor nucleus be diploid. An aneuploid or polyploidy donor cell will not permit development of the cloned nonprimate mammal. In

addition, Clark teaches that about 45-population doubling are required to generate targeted cells (Clark, page 268, col. 2, parag. 1, lines 1-5).

Applicant argues both Clark and Denning show that a fibroblast culture of transgenic cell can be established prior to senescence. Applicant argues Clark states a population of senescent donor cells can be used. Applicant argues nuclear transfer therefore can be performed with senescent cells as nuclear donors. Applicant argues there is no requirement for selection prior to senescence. Applicant argues Clark provides a variety of cell types, including fibroblasts, cumulus cells, muscle cells and mammary epithelia that have been used for cloning experiments. These arguments are not persuasive.

Fibroblasts as nuclear donors for the production of transgenic nonhuman animals are not an issue for enablement. However, most of applicant's cites are referring to the production of nontransgenic mammalian clones. Thus, Clark is correct in teaching cloned mammals have been produced from a variety of cell types, but none of these mammals, unlike applicant's claims, are transgenic. Transgenesis requires selection, especially if the transgenic is a KO sequence. For selection, the target cells must be capable of many rounds of selection prior to the cells senescing. This is exactly what Clark and Denning address. The unpredictable nature of cells capable of dividing sufficiently for selection of those cells containing the transgene. As for Clark's comment regarding senescent cells, the Lanza paper referred to does not address the production of transgenic mammals by nuclear transfer. Lanza found cells near senescence where successful nuclear donors, but these cells did not contain a transgene. Further, applicant's claims have a selection step, making selection a requirement for the claimed method.

Claims 112 and 118 remain not enabled for nuclear transfer when a neural cell is the nuclear donor. At the time of filing, the art taught mice could not be produced by nuclear

transfer using a neural cell as nuclear donor for unknown reasons (Wakayama, page 373, col. 1, parag. 1, lines 1-2).

Applicant argues after Wakayama a report appeared in the art, Kawase, establishing the use of neural cells as donor cell in nuclear transfer methods. This argument is not persuasive.

Kawase, as evidenced by the abstract, produced mouse ES cells isolating ICM cells from a mouse NT blastocyst where the blastocyst was produced by nuclear transfer using a mouse neural cell as nuclear donor. The claims are to producing a transgenic nonhuman animal. As Kawase did not produce a term mouse, Kawase does not overcome the teachings of Wakayama.

Thus, at the time of filing the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of recloning where donor cells were selected and analyzed for at least the presence of a transgene. The closest prior art U.S. Patent 6,252,133 (parag. 54) and U.S. Patent 6,011,197 (parag. 142).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch, Ph.D./
Primary Examiner, Art Unit 1632

April 17, 2008